ATENT COOPERATION TRE TY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/US2004/023793	International filing date *(day/month/year)* 22.07.2004
Priority date *(day/month/year)* 22.07.2003	
International Patent Classification (IPC) or both national classification and IPC C07D251/46, C07D401/14, C07D403/04, C07D251/42, C07D401/04, C07D239/46, C07D413/04, C07D251/16,	
Applicant NEUROGEN CORPORATION	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Fazzi, R Telephone No. +49 89 2399-8510

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/023793

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The following document has not been furnished:

   ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 60-72, 77-101

because:

☒ the said international application, or the said claims Nos. 60-72 and 77-101 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-180 (part)
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-180 (part)
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-59, 71-76, 102-180
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1) Reference is made to the following documents:

D1: WO 03/101980 A
D2: WO 03/024926 A
D3: WO 99/50256 A
D4: MATHIAS J P ET AL: "SELF-ASSEMBLY THROUGH HYDROGEN BONDING: PERIPHERAL CROWDING- A NEW STRATEGY FOR THE PREPARATION OF STABLE SUPRAMOLECULAR AGGREGATES BASED ON PARALLEL, CONNECTED CA3.M3 ROSETTES" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 116, 1994, pages 4326-4340, XP000942081 ISSN: 0002-7863

1.1) In view of its publication date of 11/12/2003 the content of D1 will not be taken into consideration in the present Written Opinion **(Reference to section VI)**.

2) Incomplete search

As already underlined in the Search Report, present claims 1, 28 and 43 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely the examples of the description, wherein A and B are -CH, R_{2a} and R_4 are hydrogen atoms and R_2 is a substituted carbon atom.

Moreover it is not clear why there can be present up to 2 R_1 substituents when F, E and D are independently CH or N. From these definitions it appears that R_1 should be positioned between R_{1a} and F and can thus be present once or absent.
Nevertheless the ring containing F, E and D has been searched as being optionally substituted and optionally condensed with further rings.

Consequently, present documents D1-D4 do not represent a complete state of the art and any statement regarding novelty and inventive step is referred to those compounds which were actually searched, as above-mentioned (this will be indicated as claims 1-180 (part)).

3) Reference to section III

Claims 60-72 and 77-101 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

4) Novelty (Reference to section V)

D2 discloses some triazine derivatives, which do not overlap with compounds presently claimed in view of the different heterocyclic groups attached to the central triazine.

D3 describes 1,3,5-triazine derivatives, which are structurally related to present compounds (cf. for instance table 3 on page 29 of D3). However said compounds of D3 do not overlap with present claims 1, 28 and 43 in view of the different substituents on the heterocyclic groups.

Compounds 23 and 24 on page 4330 of D4 are also structurally similar to present compounds, but they do not fall into the definition of claims 1, 28 and 43 because of the presence of the group -NH-Boc, which has apparently not been given for current R_1 and R_{1a} substituents.

Accordingly, the subject-matter of present claims 1-180 (part) meets the requirements of Article 33(2) PCT.

5) Inventive step (Reference to section V)

The problem to be solved by the present application may be seen as the provision of further triazine derivatives, which modulate, preferably inhibit, VR1 activation. The compounds thus obtained may be used for treating i.a. pain, cough, hiccup, urinary incontinence or overactive bladder.
None of the cited documents discloses the same technical problem (D2 describes compounds to be used against restenosis and atherosclerosis, while D3 relates to 1,3,5-triazine derivatives for treating subjects suffering from HIV).
Thus, the compounds disclosed in the present application do not appear to have been suggested by the cited documents.
The Applicant has given in table I on page 53 of the description a reasonable number of tested compounds, proving that the claimed compounds are indeed a solution of the above-mentioned technical problem.

Consequently, the subject-matter of claims 1-180 (part) meets the requirements of Article

33(3) PCT.

6) Industrial applicability (Reference to section V)

For the assessment of the present claims 60-72 and 77-101 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7) Clarity (Reference to section VIII)

7.1) Prodrug: protection cannot be sought for speculative compounds, which have yet to be prepared and investigated. Although there is an indication within the application as to what it may be, a prodrug is not a definable term as regards its structure. The skilled person has no indication as to what falls within this definition, and it should thus be deleted. No analysis of novelty and inventive step has therefore been made for all the compounds which are combinations of "prodrug" and of derivatives of current claims.

7.2) Although claims 113-180 have been drafted as separate independent claims, they appear to relate effectively to the same subject-matter and to differ from each other only with regard to the definition of the subject-matter for which protection is sought. The aforementioned claims therefore lack conciseness and as such do not meet the requirements of Article 6 PCT.

7.3) Claim 10 defines R_7 as being i.a. a hydrogen atom, which is however not in line with claim 1, which claim 10 refers to.

7.4) The description is not in conformity with the claims as required by Rule 5.1(a)(iii) PCT.